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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,179	07/11/2003	Bernard F. Erlanger	64081/JPW/AJM/MVM	4371

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EXAMINER	
WANG, LOUISE Z	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,179	ERLANGER ET AL.	
	Examiner	Art Unit	
	Louise Wang	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *6,7,12,19-36,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-11,13-18,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *18 January 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

This Office Action is in response to the Election filed on 22 August 2005. Applicant's election with traverse of Group I, claims 1-18, 37, and 38, in the reply is acknowledged. The traversal is on the grounds that the inventions of Groups I-VIII are not independent, and that the Examiner has not established that there would be a burden in examining the different groups together. This is not found persuasive because Applicant cited the "independent" but ignored the "distinct" prong of U.S.C. §121. There are two criteria for a proper requirement for restrictions between patentably distinct inventions:

(A) The inventions must be independent (see MPEP § 802.01, § 804.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(i)); and

(B) There must be a serious burden on the examiner if restriction is required (see MPEP § 803.02, § 806.04(a) - § 806.04(i), § 808.01(a), and § 808.02).

Under M.P.E.P. § 806.05, where two or more related inventions are being claimed, the principal question to be determined in connection with requirement to restrict is whether or not the inventions are distinct. The claimed inventions are distinct from each other as indicated in the prior office action on pages 4 to 7. The compositions as claimed in Inventions I and II are distinct because the antibody-peptide composition as claimed in Invention II has a second agent, which can alter the physical structure, binding specificity, and mode of action of the composition. Applicant's statement that all the compositions share the same basic structure is incorrect due to

the complexity of the second moiety in the composition of Invention II. The methods as claimed in Inventions III-VIII are distinct with respect to starting material, objectives, protocol, and end products. Therefore, each Group is patentably distinct.

Under MPEP § 808.02, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation of a different field of search. As indicated in the prior office action on page 5, the search for the Inventions would not be coextensive because a different field of search would be required based upon the structurally distinct products recited and the various methods of use comprising distinct method steps.

The restriction among the different compositions and the different methods that use the claimed compositions is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 6, 7, 12, 19-36, 39, and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Claims 3 and 4 will be read to the extent of elected species.

Claims 1-5, 8-11, 13-18, 37 and 38 are being examined.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on June 27, 2003 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 13-15, 17, and 18, are rejected under 35 U.S.C. 102(b) as being anticipated by Stein *et al* (1999).

These claims are drawn to a composition comprising a peptide moiety covalently bound to an antibody wherein the peptide comprises a poly-L-arginine peptide having a nitrogen-containing side chain comprising a guanido group and wherein the peptide moiety has various ranges of length.

Stein *et al.* teaches a complex of an antibody conjugated to an HIV Tat (37-72) peptide. Since HIV Tat (37-72) is replete with Lys, Arg and $(Arg)_3$ residues and the structures of Lys and Arg contain nitrogen and guanido groups, the reference corresponds to an arginine-rich peptide covalently linked to an antibody, meeting the limitation of "a peptide moiety comprising an amino acid residue having a nitrogen-containing side chain" as recited in claim 1, the limitation of "wherein the nitrogen-containing side chain comprises a guanido group" as recited in claim 2, the " poly-L-

arginine" as recited in claims 3-5, and the limitations of a monoclonal antibody and polyclonal antibody as recited in claims 17 and 18. See Abstract and Materials and Methods. The HIV Tat (37-72) peptide of Stein reference is 36 amino acids long, which reads on the limitation of "at least 10 amino acid residues in length" as recited in claim 13; the limitation of "between about 10 amino acid residues and about 100 amino acid residues" as recited in claim 14; and the limitation of "between about 25 amino acid residues and about 75 amino acid residues" as recited in claim 15.

Thus, the claimed invention is anticipated by Stein *et al.*

Claims 1-5, 8-11, 13-18 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Frankel *et al.* (6,316,003).

These claims are drawn to the above mentioned composition with further limitations of molecular weight, 13 kD, within the range between 11 kD and 16 kD, and of being combined with a pharmaceutically acceptable carrier in a pharmaceutical composition.

Frankel *et al.* teaches the use of transport peptides to deliver cargo molecules (see the entire document), particularly, an antibody (see columns 115 and 116, claims 1 and 6), meeting the limitation of a monoclonal antibody and polyclonal antibody as recited in claims 17 and 18, respectively. The reference discloses transport peptides such as portions of HIV Tat protein (see column 3, lines 21-31, and SEQ ID NO's: 1-7, for example), meeting the limitations of "a peptide moiety comprising an amino acid residue having a nitrogen-containing side chain" as recited in claim 1, "wherein the

nitrogen-containing side chain comprises a guanido group" as recited in claim 2, the "poly-L-arginine" as recited in claims 3-5, the molecular weight recited in claims 8 and 9, and the various lengths recited in claims 10, 11, and 13-16. The reference also teaches pharmaceutical, prophylactic and diagnostic compositions comprising transport polypeptide-cargo conjugates (see column 3, lines 13-20; column 10, lines 66-67; column 11, lines 1-19), which is recited in claim 37.

Thus, the claimed invention is anticipated by Frankel *et al.*

Claims 1-5, 8-11, 13-16, 37 and 38. are rejected under 35 U.S.C. 102(e) as being anticipated by Rothbard *et al.* (6,306,993).

These claims are drawn to the above mentioned composition in a kit.

Rothbard *et al.* teaches compositions of transport-enhancing polymers containing guanidino side chains (see abstract, particularly, column 2, lines 45-67), specifically, poly-arginine polypeptides (column 3, lines 16-25), covalently attached to a biologically active agent for enhanced transport (see abstract and columns 9-10), which reads on the limitations of claims 1-5 and 37. The reference teaches that the use of naturally occurring L-amino acid residues in the transport polymers has the advantage that breakdown products should be relatively non-toxic to the cell or organism (column 8, lines 26-34). The reference further discloses sequences of transport peptides consisting of 4, 5, 6, 7, 8, 9, 15, 20, 25 and 30 L-arginine polymers, and a mixture of longer L-arginine polymers of up to 100 amino acids, with an average molecular weight of 12,000 Daltons (column 12, lines 1-9; columns 31-34), which reads on the different

molecular weights and peptide lengths as recited in claims 8-11, and 13-16. Finally, the reference discloses that the composition may additionally be packaged with instructions for using it (column 4, lines 36-38), which reads on "a kit comprising the composition of claim 1 and instructions for use" as recited in claim 38.

Thus, the claimed invention is anticipated by Rothbard *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-5, 8-11, 13-18, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Futaki *et al.* (February, 2001) in view of Awwad *et al.* (1994).

As mentioned above, these claims are directed to a composition comprising an antibody covalently bound to a peptide moiety, specifically, a poly-L-arginine peptide.

Futaki *et al.* describes delivery of exogenous proteins into cells using various arginine-rich peptides conjugated to carbonic anhydrase. The reference discusses the translocation activity of peptides of 4-16 arginine residues and states that eight residues, or an "octa-peptide" as recited in claim 11, would be an optimal number for efficient translocation, see Abstract on page 5836. The reference further discusses the chemical conjugation of carbonic anhydrase to poly-arginine peptides, see Experimental Procedures, last paragraph on page 5836.

Futaki *et al.* does not teach the delivery of antibody by covalent linkage to poly-L-arginine peptides, or the peptide moiety of 68 amino acids in length.

Awwad *et al.* describes the modification of antibody carbohydrates by conjugation, which corresponds to a covalent bond between a peptide and an antibody. See Abstract, and Materials and Methods.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the cargo protein covalently linked to arginine-rich peptide from carbonic anhydrase of Futaki *et al.* to an antibody, as suggested by Awwad *et al.* The person of ordinary skill in the art would have been motivated to make that modification because it improves cellular uptake of an antibody and one would have

expected success because Awwad *et al.* points out that modification of antibody by conjugation does not interfere with antibody effector functions.

Furthermore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to increase the length of the peptide to 68 amino acids as routine optimization, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

Thus, the claimed invention is *prima facie* obvious over the combined teachings of the Futaki *et al.* and Awwad *et al.*

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Wang whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

L. Wang
Patent Examiner

JEFFREY STUCKER
PRIMARY EXAMINER